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## IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

J1011 U.S. PTO  
10/08/02 3058  
02/25/02  


In re Application of: Havelund et al

Application No.: To be assigned

Group Art Unit: To be assigned

Filed: February 25, 2002

Examiner: To be assigned

For: Aggregates of Human Insulin Derivatives

INFORMATION DISCLOSURE STATEMENTCommissioner for Patents  
Washington, DC 20231

Sir:

In accordance with 37 C.F.R. 1.56, 1.97 and 1.98, Applicants submit herewith references which they believe may be material to the patentability of this application and with respect to which there may be a duty to disclose in accordance with 37 C.F.R. 1.56.

While the references may be "material" under 37 C.F.R. 1.56, it is not intended to constitute an admission that the references are "prior art" unless specifically designated as such.

The filing of this Information Disclosure Statement shall not be construed as a representation that no material references other than those listed exist or that a search has been conducted.

The references are listed in the attached PTO-1449 forms which is in accordance with the requirements of M.P.E.P. 609. Copies of the references listed in the attached 1449 forms were filed with, or cited by, the USPTO in USSN 09/193,552 filed November 17, 1998, and in 09/227,774 filed January 8, 1999, the benefit of both of which is claimed under 35 USC 120.

The references are as follows:

1. WO 97/31022
2. WO 96/04307
3. Kurtzhals et al., "Albumin Binding and Time Action of Acylated Insulins in Various Species" (1996) J. of Pharmaceutical Sciences 85(3):304-308

4. Sluzky et al., "Kinetics of Insulin Aggregation in Aqueous Solutinos Upon Agitation in the Presence of Hydrophobic Surfaces" (1991) Proc. Nat. Acad. Sci. USA 88:9377-9381
5. Katakam et al., "Aggregation of Insulin and Its Prevention by Carbohydrates Excipients" Vol. 49, No. 4, pgs. 160-165 (1995)
6. Brange et al., "Toward Understanding Insulin Fibrillation" Journal of Pharmaceutical Sciences, Vol. 86, No. 5, 517-525 (1997)
7. Samuel et al., "Studies on the Immunogenicity of protamines in humans and Animals by Means of a Micro-complement Fixation Test" Clin. Exp. Immunol., Vol. 33, pgs. 252-260 (1978)
8. File medline on STN. No. 90282737. Rafter, "Reaction of Insulin with Reduced Gluthathione", Biochemistry International, Vol. 20, pp. 817-820, (1990) (abstract only)
9. Markussen et al., "Soluble, Fatty Acid Acylated Insulins Bind to Actions in Pigs" Diabetologia, Vol. 39, pgs. 281-288 (1996)
10. Kurtzhals et al., "Albumin Binding Of Insulins Acylated With Fatty Ligand-Protein Interaction and Correlation Between Binding Affinity and Effect in Vivo" Biochem. J., Vol. 312, pgs. 725-731 (1995)
11. Eugéne Fredericq, "The Association of Insulin Molecular Units in Aqueous Solutions" Archives of Biochemistry and Biophysics, Vol. 65, pgs. 218-228 (1956)
12. Whittingham et al., "Crystal Structure of a Prolonged-Acting Insulin With Albumin-BindingProperties" Biochemistry, Vol.36, pgs.2826-2831 (1997)
13. Jeffrey et al., "Apparent Molecular Weight of Insulin in Dilute Acid Solution" Nature, Vol. 197, No. 4872, pgs. 1104-1105 (1963)
14. Blundell et al., "Three-Dimensional Atomic Structure of Insulin and Its Relationship to Activity" Diabetes 21 (Suppl. 2), pgs. 492-505 (1972)
15. Grant et al., "Differences in the Nature of the Interaction of Insulin and Proinsulin with Zinc" Biochem. J., Vol. 126, pgs. 433-440 (1972)
16. Jeffrey et al., "An Equilibrium Ultracentrifuge Study of the Self-Association of Bovine Insulin" Biochemistry, Vol. 5, No. 12, pgs. 3820-3824 (1966)
17. Jeffrey et al., " An Equilibrium Ultracentrifuge Study of the Self – Association of Bovine Insulin" Biochemistry, Vol. 5, No. 2, pgs. 489-498 (1966)
18. Blundell et al., "III. Aggregation: Nature of the Forces, Crystal Structure, and Physiological State" Adv. Protein Chem., Vol. 26, pgs. 297-330 (1972)
19. Kurtz et al., "Circulating IgG Antibody to Protamine in Patients Treated with Protamine-Insulins: Diabetologia, Vol. 25, pgs. 322-324 (1983)
20. WO 91/12817
21. WO 96/00107
22. WO 95/07931
23. US 5,866,538
24. US 6,011,007
24. File Medline on STN. No. 90282737. Rafter, G.W. "Reaction of Insulin With Reduced Gluthathione Biochemistry International, Vol. 20, No. 4 pgs. 817-820 1990 (Abstract Only)

It is respectfully requested that these references be considered by the Patent and Trademark Office in its examination of the above-identified application and be made of record therein. The Examiner is also invited to contact the Undersigned if there are any questions concerning this paper.

The Information Disclosure Statement submitted herewith is being filed on the filing date of the application. Therefore, no fee is due.

Respectfully submitted,

Date: February 25, 2002

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PATENT TRADEMARK OFFICE

FORM PTO-1449  
(Rev. 2-32)U.S. DEPARTMENT OF COMMERCE  
PATENT AND TRADEMARK OFFICE

Atty. Docket No. 5386.224-US

Serial No. To be assigned

INFORMATION DISCLOSURE  
STATEMENT BY APPLICANT  
(Use several sheets if necessary)

Applicant Havelund et al

Filing Date February 25, 2002

Group To be assigned

J1911 U.S. 083058  
02/25/02

## U.S. PATENT DOCUMENTS

EXAMINER INITIAL	DOCUMENT NUMBER	DATE	NAME	CLASS	SUBCLASS	FILING DATE IF APPROPRIATE
	5,866,538	02/02/99	Norup et al	514	3	06/20/97
	6,011,007	01/04/00	Havelund et al	514	3	11/20/97

## FOREIGN PATENT DOCUMENTS

	DOCUMENT NUMBER	DATE	COUNTRY	CLASS	SUBCLASS	TRANSLATION	
						YES	NO
	WO 97/31022	08/28/97	WIPO				
	WO 96/04307	02/15/96	WIPO				
	WO 91/12817	09/05/91	WIPO				
	WO 96/00107	01/04/96	WIPO				
	WO 95/07931	03/23/95	WIPO				

## OTHER DOCUMENTS (Including Author, Title, Date, Pertinent Pages, Etc.)

		Kurtzhals et al., "Albumin Binding and Time Action of Acylated Insulins in Various Species" Journ of Pharmaceutical Sciences, Vol. 85, No. 3 , pgs. 304-308(1996)
		Sluzky et al., "Kinetics of Insulin Aggregation in Aqueous Solutions Upon Agitation In the Presence of Hydrophobic Surfaces" Proc. Nat. Acad. Sci. USA Vol. 88, pgs. 9377-9381 (1991)
		Katakam et al., " Aggregation of Insulin and Its Prevention by Carbohydrates Excipients", PDA Journal of Pharmaceutical Science & Technology, Vol. 49, No. 4, pgs. 160-165 (1995)
		Brange et al., "Toward Understanding Isulin Fibrillation" Journal of Pharmaceutical Sciences. Vol. 86, No. 5 pgs. 517-525 (1997)
		Samuel et al.. "Studies on the immunogenicity of protamines in humans and experimental animals by means of a micro-complement fixation test". Clin. Exp. Immunol Vol.33, pgs. 252-260(1978) File medline on STN. No. 90282737. Rafter, "Reaction of Insulin with Reduced Gluthathione", Biochemistry International, Vol. 20, pp. 817- 820, (1990) (abstract only)

EXAMINER

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		DOCUMENT NUMBER	DATE	COUNTRY	CLASS	SUBCLASS	TRANSLATION	
							YES	NO

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		Markussen et al., "Soluble, fatty acid acylated insulins bind to action in pigs" Diabetologia, Vol. 39, pgs. 281-288 (1996)
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		Ligand-protein interaction and correlation between binding affinity and
		Effect in vivo" Biochem J. Vol. 312, pgs. 725-731 (1995)
		Eugéne Fredericq, "The Association of Insulin Molecular Units in
		Aqueous Solutions" Archives of Biochemistry and Biophysics, Vol. 65
		pgs. 218-228 (1956)
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**U.S. PATENT DOCUMENTS**

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	Blundell et al., "Three-Dimensional Atomic Structure of Insulin and Its Relationship to Activity Diabetes 21 (Suppl. 2), pgs. 492-505 (1972);
	Grant et al., "Differences in the Nature of the Interaction of Insulin and Proinsulin with Zinc" Biochem. J., Vol. 126, pgs. 433-440 (1972);
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